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September 16, 1992

Document Processing Center (TS-790)
Office of Pollution Prevention and Toxics
U. S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460
Attn: Section 8(e) Coordinator (CAP Agreement)

Dear Sir or Madam:

Subject: Report submitted in accordance with guidelines established by the U. S. Environmental Protection Agency Registration and Agreement for the TSCA 8(e) Compliance Audit Program

Report submitted by: Eastman Kodak Company
343 State Street
Rochester, NY 14650
(716) 724-4000
CAP Agreement Identification Number (8ECAP-0039)

The report pertains to thiophene [CAS #110-02-1] and is being submitted because of effects observed during a study conducted by multiple routes of exposure. The title of the report being submitted is: "Basic Toxicity of Thiophene". The report is being identified as a study involving other than human effects (Unit II.B.2.b of CAP Agreement).

Groups of five male rats were administered one to thirteen doses of the test compound by gavage at 50, 100, 500 or 1,000 mg/kg over nineteen days. Feed intake and body weight gain were decreased at the 500 and 1,000 mg/kg dose levels. Four animals from the high-dose group either died or were euthanatized in poor condition by study Day 2. Abnormalities observed at the two highest doses included central nervous system toxicity, hematology and clinical chemistry changes, increased relative liver weights, and hepatic necrosis. Thymic cortical atrophy, splenic lymphoid depletion, and hypocellular bone marrow were observed in one animal in the high-dose group. No gross or histopathologic changes were observed at the two lowest dose levels.

Groups of five male rats were exposed by inhalation to 1,600 or 3,200 ppm of the test compound six hours per day for two to twelve exposures over a fifteen day period. Feed intake and body weight gain were decreased at both dose levels. Abnormalities observed at both dose levels included central nervous system toxicity, decreased absolute kidney and epididymis weights, and increased relative liver weights. Gross and histopathologic changes observed at the high-dose level included: pale, yellow mottled livers; hematuria; hepatic necrosis; nephrosis; rhinitis; and necrotic thymiditis.

3/9/95

The results of these studies have been published in ***Neurotoxicity of Industrial and Commercial Chemicals, Volume 2***. J.L. O'Donoghue, Editor. CRC Press, Boca Raton, Florida. p. 50 (1985).

The test compound has been used internally and sold as a pure chemical; sales volumes have been less than 120 kg/year.

Questions regarding this submission should be addressed to:

Mr. William Hart
Eastman Kodak Company
Corporate Health and Environment Laboratories
Rochester, NY 14652-3615
(716) 722-5991

Sincerely,

R. Hays Bell

R. Hays Bell, Ph.D.
Vice President
Corporate Health, Safety and Environment
(716) 722-5036

RHB:DRG
Enclosure

114486H

TX-79-117

Basic Toxicity of Thiophene

Toxicology Section

Written by: John L. O'Donoghue, V.M.D., Ph.D.

August 22, 1979

Basic Toxicity of Thiophene

The oral LD_{50} in male rats was 1131 mg/kg and in male mice was 1902 mg/kg. When applied to the depilated abdomens of guinea pigs under an occlusive wrap for 24 hours, strong irritation developed but absorption through the skin was not evident. Repeated application to the dorsum of guinea pigs by rub-on moderately exacerbated the irritative response. The material apparently defatted the skin. When tested by a standardized skin sensitization test, none of the five guinea pigs tested were sensitized. Although eye irritation tests were not conducted, based on the strong skin irritation observed in guinea pigs, this compound would be expected to be an eye irritant. The acute inhalation 6 hour LC_{50} in rats was ~525 ppm.

Data supplied by the Pennwalt Corporation stated that on rabbit skin refined Thiophene was a non-irritant with no evidence of percutaneous absorption and that the one-hour inhalation LC_{50} in mice was 2660 ppm.

Groups of male rats were administered 50, 100, 500 and 1000 mg/kg/day of the test compound by gavage. Control groups received distilled water. At 500 and 1000 mg/kg, weight gain was severely depressed and feed intake was depressed moderately in the 500 mg/kg rats and severely in 1000 mg/kg rats. At 50 and 100 mg/kg, these parameters were comparable to controls except for slight increases in weight gain and feed intake in 50 mg/kg rats.

Clinical abnormalities were present in the two highest doses but not in the other groups. In the 1000 mg/kg group, one rat died within 24 hours of the first dose, and three additional rats were killed on the second day in poor condition thus, only one rat survived to the end of the study.

The three rats that were killed were weak, staggered, twitched, showed head tremors or showed abnormal limb jerking, which are indications of central nervous system toxicity. In the 500 mg/kg group, two rats were weak, staggered and twitched.

Hematology and clinical chemistries were abnormal at 500 and 1000 mg/kg but not at other doses. Rats from the 1000 mg/kg group showed a moderate decrease in hemoglobin and hematocrit. The white cell count was normal but the differential smear showed spherocytosis, anisocytosis, changes in red cell size, increased polychromasia, poikilocytosis, decreased number of platelets, large platelets and toxic granulation in segmented white blood cells. At 500 mg/kg, hemoglobin and hematocrit were normal while the white cell count was slightly elevated. The differential smear showed anisocytosis and poikilocytosis.

Serum clinical chemistries were also abnormal only in the two highest groups. In the 1000 mg/kg group, glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), and lactic dehydrogenase (LDH) were markedly elevated. Urea nitrogen was moderately elevated. In the 500 mg/kg group GOT and GPT were moderately elevated and alkaline phosphatase was slightly depressed. Sera were icteric in the 1000 mg/kg group only. These changes are indicative of both hepatic and renal damage in the 1000 mg/kg group and hepatic damage in the 500 mg/kg group.

Organ weights were affected by the compound only in the two highest dose groups. Absolute liver weights were slightly elevated in the 1000 mg/kg group and slightly depressed in the 500 mg/kg group but on a relative basis both dose levels increase liver weight markedly in the 1000 mg/kg dose level and moderately in the 500 mg/kg dose level. Relative kidney but not absolute

kidney weights were slightly elevated in the 1000 mg/kg group. Absolute kidney weight in the 500 mg/kg group was slightly lower but in line with the lower body weight therefore on a relative basis was comparable to controls.

Gross pathology showed hemorrhage in the stomach and testes only in the 1000 mg/kg group. Histologically, hepatic necrosis was present in the 500 and 1000 mg/kg groups and one rat in the 1000 mg/kg group showed thymic cortical atrophy, splenic lymphoid depletion and hypocellular bone marrow. Pathologic examinations in the remaining animals were normal.

A second study was performed to examine the effects of thiophene by the inhalation route of exposure. Groups of five male rats were exposed to 1600 and 3200 ppm of the test compound or conditioned air six hours per day for 12 exposures over a 15 day period. At both exposure levels weight gain and feed intake were severely depressed. At 3200 ppm the animals were drowsy, showed slight weakness, lacrimated following first few exposures, showed alterations in respiratory rate following the first few exposures, and developed slight tremors until the third day of the test, and whole body twitching. One rat died on the second exposure day. At 1600 ppm clinical signs included tremors, drowsiness, lack of grooming, weakness and polyphyrin tears.

Hematologic determinations (hemoglobin, hematocrit, white blood cell count and differential cell counts) were comparable to controls except for a moderate decrease in white cell count in the 3200 ppm group.

Clinical chemistries (glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, lactic dehydrogenase, alkaline phosphatase, urea

nitrogen and glucose) were comparable to control values.

Absolute liver weight in the 3200 ppm group was slightly depressed and was normal in the 1600 ppm group but relative liver weight was slightly increased in both groups. Absolute kidney weights and epididymis weights were slightly depressed but based on relative weight, they were comparable to controls. Absolute and relative testis weights were comparable to controls for both test groups.

On autopsy examination one treated animal showed a pale, yellow mottled liver and a urinary bladder filled with dark brown urine most likely due to blood pigments. All other animals were unremarkable. Histologically, this same animal showed severe hepatic necrosis, minimal nephrosis, minor necrobiotic changes in the thymus and minor focal necrotic rhinitis. All other animals were unremarkable.

In addition to this work, the literature cited on the summary sheets indicates that thiophene is neurotoxic in dogs and rats producing acute cerebellar granular cell necrosis.

Sites of toxic action for thiophene include the liver, kidney, lymphoid tissue, red blood cell, circulating granulocytes and central nervous system by systemic routes and the nasal passages by local administration

The static 96 hour LC_{50} for fathead minnows was 100 µl/l and for daphnids, snails, flatworms and gammarus was >100 µl/l. The no-effect concentration on germination, hypocotyl growth and root growth of ryegrass, radish and lettuce was 100 µl/l. The Industrial Laboratory, Kodak Park, determined the chemical oxygen demand to be 1.6 gO_2/ml of sample. Total and biological oxygen demands were not determined due to poor water miscibility.

JO'D:ijp

SUMMARY OF BASIC TOXICITY

Chemical Thiophene

Date 7/23/79

LD50 (mg/kg) P.O. Rats 1131(700-1829) Mice 1902 (1354-2672)

Remarks: Clinical signs included rough hair coat, weakness, tremors and ataxia.

Guinea Pig Skin Irritation (covered) LD50 >20 ml/kg Absorption: Evident

Slight Moderate Strong Severe Not evident

Remarks:

Rabbit Eye Irritation ND

Slight Moderate Strong Fluorescein stain: Cornea Adnexa

No. washed

No. unwashed

Remarks: Based on the results of the skin irritation test, this compound would be expected to produce eye irritation.

Skin Sensitization Potential No. guinea pigs 5

None 4/5 Weak 1/4 Moderate Potent

Remarks:

Repeated (10 days) Skin Application (uncovered) No. guinea pigs 5

Remarks: Repeated application moderately exacerbated the irritative response.

Acute Inhalation LC50 mg/m^3 (ppm) Rats 4525 ± 0

OTHER TESTS: Data from Pennwalt Corporation:
Rabbit skin irritation test: non-irritant, no evidence of absorptic
One hour inhalation LC_{50} in mice: 2660 ppm
API TOXICOLOGICAL REVIEW:
Repeated daily injection of 2g of Thiphene in dogs resulted in locomoter ataxia and paralysis.

Bradley, P. and Berry, M. Effects of thiophene on the purkinje cell dendritic tree: a quantitative golgi study. Neuropathol. Appl. Neurobiol. 5:9-16, 1979. Repeated exposure to rats resulted in complete elimination of granular cells in some areas of the cerebellum.

Other Tests: (continued)

Albrechtsen, R. and Jensen, H. Histochemical investigation of thiophene necrosis in the cerebellum of rats. Acta Neuropathol. 26:217-223, 1973.

Thiophene produced selective cerebellar granular cell necrosis when repeatedly administered by subcutaneous injection in rats.

SUMMARY OF BASIC TOXICITY-- 3

Repeated Exposure Feeding Drinking Water Gavage Inhalation

No. rats/group 5 No. exposures 1-13 No. days 19 Carrier None

Units of exposure: % mg/kg mg/m^3 ppm

Exposure concentration:	1000	500
Weight gain	↓3	↓3
Feed intake	↓3	↓2
Daily dose (mg/kg/day)	1000	500
Signs/behavior	Ab See Text	Ab

Hematology:	1000	500
Hgb.	↓2	N
Hct.	↓2	N
WBC	N	↑ 1
Diff.	Ab See Text	Ab

Clinical chemistry:

GOT	↑3	↑2
GPT	↑3	↑2
LDH	↑3	N
AP	N	↓1
UN	↑2	N
Glucose	N	N

Organ weight:

	1000	500
Liver		
Abs.	↑1	↓ 1
Rel.	↑3	↑ 2
Kidney		
Abs.	N	↓ 1
Rel.	↑1	N

At 1000 mg/kg the serum was icteric.

Gross pathology: 100 mg/kg: hemorrhage in the stomach and testes

Histopathology: 500 and 1000 mg/kg: Hepatic necrosis
1000 mg/kg: one rat showed cortical atrophy of the thymus and hypocellularity of the bone marrow and lymphoid follicles of the spleen.

Site of toxic action: Liver, lymphoid tissue, kidney, central nervous system, red blood cell, circulating granulocytes.

Legend

↑	Increased
↓	Decreased
1	Slight
2	Moderate
3	Great
N	Normal
ND	Not done

4/79:bdo

SUMMARY OF BASIC TOXICITY-- 4

Repeated Exposure Feeding Drinking Water Gavage Inhalation

No. rats/group 5 No. exposures 12 No. days 18 Carrier NONE

Units of exposure: % mg/kg mg/m^3 ppm

Exposure concentration:	100	50		100	50
Weight gain	N	↑1	Hematology:		
Feed intake	N	↑1	Hgb.	N	N
			Hct.	N	N
Daily dose (mg/kg/day)	100	50	WBC	N	N
			Diff.	N	N
Signs/behavior	N	N			

Clinical chemistry:			Organ weight:		
GOT	N	N	Liver		
GPT	N	N	Abs.	N	↑1
LDH	N	N	Rel.	N	N
AP	N	N	Kidney		
UN	N	N	Abs.	N	N
Glucose	N	N	Rel.	N	N

Gross pathology: No compound related changes identified.

Histopathology: No compound related changes identified.

Site of toxic action: See other sheets

Legend

↑	Increased
↓	Decreased
1	Slight
2	Moderate
3	Great
N	Normal
ND	Not done

4/79:bdo

SUMMARY OF BASIC TOXICITY--5

Repeated Exposure | Feeding | Drinking Water | Gavage | Inhalation

No. rats/group 5 No. exposures 12 No. days 15 Carrier NONE

Units of exposure: ~~mg/kg~~ ~~mg/m³~~ (ppm)

Exposure concentration:	3200	1600		3200	1600
Weight gain	↓3	↓3	Hematology:		
Feed intake	↓3	↓3	Hgb.	N	N
			Hct.	N	N
Daily dose (mg/kg/day)	---	---	WBC	↓2	N
			Diff.	N	N
Signs/behavior	Ab	Ab			

See text

Clinical chemistry:			Organ weight:		
SGOT	N	N	Liver		
GPT	N	N	Abs.	↓1	N
LDH	N	N	Rel.	↑1	↑1
AP	N	N	Kidney		
UN	N	N	Abs.	↓2	↓2
Glucose	N	N	Rel.	N	N
			Testes		
			Abs.	N	N
			Rel.	N	N
			Epididymis:		
			Abs.	↓1	↓1
			Rel.	N	N

Gross pathology: 3200 ppm: liver mottled, yellow, hematuria in 1/5 rats.

Histopathology: 3200 ppm: hepatic necrosis, nephrosis, necrotic thymiditis, rhinitis in 1/5 rats.

Site of toxic action: Liver, kidney, thymus, nasal passages, central nervous system.

Legend

↑	Increased
↓	Decreased
1	Slight
2	Moderate
3	Great
N	Normal
ND	Not done

4/79:bdo

SUMMARY OF BASIC TOXICITY -- 6

Static 96 hour LC_{50} µl/l Gammarus >100

Fathead minnows 100 Daphnids >100 Snails >100 Flatworms >100

No effect concentration - µl/l

	Germination	Hypocotyl Growth	Root Growth
Ryegrass	100	100	100
Radish	100	100	100
Lettuce	100	100	100

Remarks: The compound was not miscible in water.

Industrial Laboratory (g O_2/ml sample)

BOD_5 ND BOD_2 ND TOD ND COD 1.6

The test compound was not miscible with water.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

R. Hays Bell, Ph.D.
Vice President, Corporate Health, Safety, and Environment
Eastman Kodak Company
343 State Street
Rochester, New York 14650

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MAY 0 8 1995

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000) assigned by EPA to your submission(s). Please cite the assigned 8(e) number when submitting follow-up or supplemental information and **refer to the reverse side of this page for "EPA Information Requests"** .

All TSCA 8(e) submissions are placed in the public files unless confidentiality is claimed according to the procedures outlined in Part X of EPA's TSCA §8(e) policy statement (43 FR 11110, March 16, 1978). Confidential submissions received pursuant to the TSCA §8(e) Compliance Audit Program (CAP) should already contain information supporting confidentiality claims. This information is required and should be submitted if not done so previously. To substantiate claims, submit responses to the questions in the enclosure "Support Information for Confidentiality Claims". This same enclosure is used to support confidentiality claims for non-CAP submissions.

Please address any further correspondence with the Agency related to this TSCA 8(e) submission to:

Document Processing Center (7407)
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, D.C. 20460-0001

EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

Sincerely,

Terry R. O'Bryan

Terry R. O'Bryan
Risk Analysis Branch

Enclosure

12507A

Triage of 8(e) Submissions

Date sent to triage: MAY 0 3 [illegible]

NON-CAP CAP

Submission number: 12507A

TSCA Inventory: Y N D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX SBTOX SEN w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX	CTOX	EPI	RTOX	GTOX
STOX/ONCO	CTOX/ONCO	IMMUNO	CYTO	NEUR

Other (FATE, EXPO, MET, etc.): _____

Notes:

THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY

For Contractor Use Only

entire document: 0 (1) 2 **pages** 42 **pages** 42, DMBS

Notes:

Contractor reviewer : PR **Date:** 4/26/95

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA: Submission # 8EHQ- 0992-12507 SEQ. A

TYPE: (INT.) SUPP FLWP

SUBMITTER NAME: Eastman Kodak Company

SUB. DATE: 09/16/92 OTS DATE: 09/24/92 CSRAD DATE: 03/09/95

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0639) REFER TO CHEMICAL SCREENING
(0678) CAP NOTICE

VOLUNTARY ACTIONS:
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKER ACTIVITIES
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP/USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

CHEMICAL NAME:

CAS#
110-02-1

INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04
0202	ONCO (ANIMAL)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04
0204	MUTA (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04
0207	REPRO/TERATO (ANIMAL)	01 02 04
0208	NEURO (HUMAN)	01 02 04
(0209)	NEURO (ANIMAL)	01 (02) 04
0210	ACUTE TOX. (HUMAN)	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04
0212	ACUTE TOX. (ANIMAL)	01 02 04
(0213)	SUB ACUTE TOX (ANIMAL)	01 (02) 04
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04
0215	CHRONIC TOX (ANIMAL)	01 02 04

INFORMATION TYPE:		P F C
0216	EPI/CLIN	01 02 04
0217	HUMAN EXPOS (PROD CONTAM)	01 02 04
0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0219	HUMAN EXPOS (MONITORING)	01 02 04
(0220)	ECO/AQUA TOX	01 (02) 04
0221	ENV. OCCC/REL/FATE	01 02 04
0222	EMER INCI OF ENV CONTAM	01 02 04
0223	RESPONSE REQEST DELAY	01 02 04
0224	PROD/COMP/CHEM ID	01 02 04
0225	REPORTING RATIONALE	01 02 04
0226	CONFIDENTIAL	01 02 04
0227	ALLERG (HUMAN)	01 02 04
(0228)	ALLERG (ANIMAL)	01 (02) 04
0239	METAB/PHARMACO (ANIMAL)	01 02 04
0240	METAB/PHARMACO (HUMAN)	01 02 04

INFORMATION TYPE:		P F C
0241	IMMUNO (ANIMAL)	01 02 04
0242	IMMUNO (HUMAN)	01 02 04
0243	CHEM/PHYS PROP	01 02 04
0244	CLASTO (IN VITRO)	01 02 04
0245	CLASTO (ANIMAL)	01 02 04
0246	CLASTO (HUMAN)	01 02 04
0247	DNA DAM/REPAIR	01 02 04
(0248)	PROD/USE/PROC	01 02 04
0251	MSDS	01 02 04
0299	OTHER	01 02 04

Atox | Sbtox | Sen | Neur

TRIAGE DATA: NON-CBI INVENTORY
(YES)
CAS SR NO
(N TRIAMINI

ONGOING REVIEW
YES (DROP/REFER) Fish, RAT, MUS
NO (CONTINUE) Daphnids, SP, RBT
REVIEW

SPECIES

TOXICOLOGICAL CONCERN:
(LOW)
(MED)
HIGH

USE: internal

PRODUCTION: Sales < 120 kg/yr

> <ID NUMBER>
8(e)-12507A

> <TOX CONCERN>
M/L

> <COMMENT>
ACUTE ORAL TOXICITY IN RATS IS LOW CONCERN WITH MALE RAT AND MALE MOUSE LD50S OF 1131 AND 1902 MG/KG, RESPECTIVELY. NO DOSE LEVELS OR NUMBER OF ANIMALS USED IN THE TEST ARE GIVEN. CLINICAL SIGNS INCLUDED ROUGH COAT, WEAKNESS, TREMORS, AND ATAXIA.

SKIN IRRITATION IN GUINEA PIGS IS MEDIUM CONCERN. THE NUMBER OF ANIMALS WAS NOT GIVEN. THE TEST MATERIAL PRODUCED STRONG IRRITATION BUT NO EVIDENCE OF ABSORPTION.

ACUTE DERMAL TOXICITY IN GUINEA PIGS IS LOW CONCERN WITH AN LD50 OF > 20 ML/KG.

REPEATED SKIN APPLICATION IN GUINEA PIGS IS LOW CONCERN. WHEN 5 ANIMALS WERE TREATED, THE TEST MATERIAL MODERATELY EXACERBATED THE IRRITATIVE RESPONSE.

SKIN SENSITIZATION IS LOW CONCERN IN GUINEA PIGS. 1 ANIMAL HAD A WEAK REACTION TO THE TEST MATERIAL.

ACUTE INHALATION TOXICITY IN RATS IS LOW CONCERN WITH AN LC50 OF 4525 PPM FOR A 6 HOUR EXPOSURE.

SKIN IRRITATION IN RABBITS IS LOW CONCERN. THE TEST MATERIAL WAS NONIRRITATING AND EXHIBITED NO EVIDENCE OF SKIN ABSORPTION.

ACUTE INHALATION TOXICITY IN MICE IS LOW CONCERN WITH AN LC50 OF 2660 PPM FOR A 1 HOUR EXPOSURE.

REPEATED DAILY INJECTIONS IN DOGS IS LOW CONCERN. 2 G OF TEST MATERIAL CAUSED LOCOMOTOR ATAXIA AND PARALYSIS.

A REPEATED SUBCUTANEOUS INJECTION STUDY WAS DONE IN RATS. THE TEST MATERIAL PRODUCED SELECTIVE CEREBELLAR GRANULAR CELL NECROSIS.

SUBACUTE ORAL TOXICITY IN MALE RATS IS MEDIUM CONCERN. ANIMALS WERE EXPOSED TO FOUR DOSE LEVELS: 50, 100, 500, AND 1000 MG/KG. RATS WERE EXPOSED TO 50 AND 100 MG/KG FOR 12 EXPOSURES OVER 15 DAYS AND NO COMPOUND-RELATED CHANGES OCCURRED AT THESE LEVELS. RATS WERE EXPOSED TO 500 AND 1000 MG/KG FOR 13 EXPOSURES OVER 19 DAYS AND 4 OUT OF 5 ANIMALS DIED AT 1000 MG/KG. CLINICAL SIGNS INCLUDED WEAKNESS, STAGGERING, TWITCHING, HEAD TREMORS, ABNORMAL LIMB JERKING (INDICATING CNS TOXICITY), AND DECREASED WEIGHT GAIN AND FOOD INTAKE. THERE WERE HEMATOLOGICAL, CLINICAL CHEMISTRY, AND ORGAN WEIGHT CHANGES NOTED. GROSS PATHOLOGY REVEALED HEMORRHAGE IN STOMACH AND TESTES (1000 MG/KG) AND HEPATIC NECROSIS AT BOTH DOSE LEVELS. SITE OF TOXIC ACTION WAS IN THE LIVER, LYMPHOID TISSUE,

KIDNEYS, RBC, AND CIRCULATING GRANULOCYTES.

SUBACUTE INHALATION TOXICITY IN RATS IS LOW CONCERN FOR A 6 HOUR EXPOSURE. 10 ANIMALS (5/GROUP) WERE EXPOSED 12 TIMES OVER 15 DAYS TO EITHER 1600 OR 3200 PPM. THERE WAS 1 MORTALITY AT 3200 PPM. CLINICAL SIGNS INCLUDED DEPRESSED WEIGHT GAIN AND FOOD INTAKE, DROWSINESS, SLIGHT WEAKNESS, LACRIMATION, ALTERATIONS IN RESPIRATORY RATE, SLIGHT TREMORS, WHOLE BODY TWITCHING, LACK OF GROOMING, AND POLYPHYRIN TEARS. HEMATOLOGIC AND ORGAN WEIGHT CHANGES WERE NOTED. PATHOLOGIC EXAM REVEALED CHANGES IN 1 ANIMAL AND CONSISTED OF LIVER AND URINARY BLADDER CHANGES, AND HEPATIC NECROSIS, NEPHROSIS, NECROTIC THYMIDITIS, AND RHINITIS. SITES OF TOXIC ACTION WERE LIVER, KIDNEY, THYMUS, NASAL PASSAGES AND CNS.